

this section for any of the indications listed, shall submit, on or before August 25, 1975 to the Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, a new drug application or a "Investigational New Drug Application" for each such drug for which the manufacturer or distributor does not have an approved new drug application pursuant to section 505(b) of the act. If the drug is a biologic, a "Investigational New Drug Application" or an application for a license under section 351 of the Public Health Service Act shall be submitted to the Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20014, in lieu of any submission to the Center for Drug Evaluation and Research.

(4) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (f)(1) of this section, in the "chemical form" and intended for the uses stated, is terminated on August 26, 1975 except as provided in paragraph (f)(5) of this section.

(5)(i) Except as provided in paragraph (f)(5)(ii) of this section, the exemption referred to in paragraph (a) of this section, as applied to any drug containing any of the isotopes listed in paragraph (f)(1) of this section, in the "chemical form" and intended for the uses stated, for which drug a new drug application or "Investigational New Drug Application" was submitted to the Center for Drug Evaluation and Research on or before August 25, 1975 is terminated on August 20, 1976, unless an approvable notice was issued on or before August 20, 1976, in which case the exemption is terminated either upon the subsequent issuance of a nonapprovable notice for the new drug application or on November 20, 1976, whichever occurs first.

(ii) The exemption referred to in paragraph (a) of this section, as applied to any biologic containing any of the isotopes listed in paragraph (f)(1) of this section in the "chemical form" and intended for the uses stated, for which biologic an application for product license or "Investigational New Drug Application" was submitted to

the Center for Biologics Evaluation and Research on or before August 25, 1975 is terminated on October 20, 1976, unless an approvable notice was issued on or before October 20, 1976, in which case the exemption is terminated either upon the subsequent issuance of a nonapprovable notice for the new drug application or on January 20, 1977, whichever occurs first.

(g) The exemption referred to in paragraph (a) of this section, as applied to any drug intended solely for investigational use as part of a research project, which use had been approved on or before July 25, 1975 in accordance with 10 CFR 35.11 (or equivalent regulation of an Agreement State) is terminated on February 20, 1976 if the manufacturer of such drug or the sponsor of the investigation of such drug submits on or before August 25, 1975 to the Food and Drug Administration, Bureau of Drugs, HFD-150, 5600 Fishers Lane, Rockville, MD 20857, the following information:

- (1) The research project title;
- (2) A brief description of the purpose of the project;
- (3) The name of the investigator responsible;
- (4) The name and license number of the institution holding the specific license under 10 CFR 35.11 (or equivalent regulation of an Agreement State);
- (5) The name and maximum amount per subject of the radionuclide used;
- (6) The number of subjects involved; and
- (7) The date on which the administration of the radioactive drugs is expected to be completed.

(h) The exemption referred to in paragraph (a) of this section, as applied to any drug not referred to in paragraphs (d), (f), and (g) of this section, is terminated on August 26, 1975.

[39 FR 11680, Mar. 29, 1974, as amended at 40 FR 31307, July 25, 1975; 40 FR 44543, Sept. 29, 1975; 41 FR 35171, Aug. 20, 1976; 41 FR 42947, Sept. 29, 1976; 50 FR 8996, Mar. 6, 1985; 55 FR 11578, Mar. 29, 1990]

§ 310.504 Amphetamines (amphetamine, dextroamphetamine, and their salts and levamfetamine and its salts) for human use.

- (a) Amphetamine and dextroamphetamine and their salts. (1)

Pursuant to the drug efficacy requirements of the Federal Food, Drug, and Cosmetic Act, the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, has evaluated certain dosage forms of amphetamines and other sympathomimetic stimulant drugs intended for use in the treatment of obesity and for other uses. The Academy found that such drugs as a class have been shown to have a generally short-term anorectic action. They further commented that clinical opinion on the contribution of the sympathomimetic stimulants in a weight reduction program varies widely, the anorectic effect of these drugs often plateaus or diminishes after a few weeks, most studies of them are for short periods, no available evidence shows that use of anorectic alters the natural history of obesity, some evidence indicates that anorectic effects may be strongly influenced by the suggestibility of the patient, and reservations exist about the adequacy of the controls in some of the clinical studies. Their significant potential for drug abuse was also cited.

(2) In addition to those dosage forms that were reviewed for efficacy by the Academy, other dosage forms of amphetamine drugs are on the market that were not cleared through the new drug procedures. While certain amphetamines were marketed prior to enactment of the Federal Food, Drug, and Cosmetic Act in 1938, some of the conditions of use subsequently prescribed, recommended, or suggested in their labeling (for example, for the treatment of obesity) differ from uses claimed for the amphetamines before said enactment. Such uses have not been cleared through the effectiveness provisions of the Drug Amendments of 1962 (Pub. L. 87-781 which amended the Federal Food, Drug, and Cosmetic Act). These drugs are very extensively used in the treatment of obesity. The extent of use for such purposes as narcolepsy and minimal brain dysfunction in children is believed to be minor as compared with the total usage of these drugs. Because of their stimulant effect on the central nervous system, they have a potential for misuse by those to whom they are available through a physician's prescription, and their abuse by

those who obtain them through illicit channels is well documented. Production data indicate that amphetamines have been produced and prescribed in quantities greatly in excess of demonstrated medical needs.

(3) Pursuant to a notice published in the FEDERAL REGISTER of August 8, 1970 (35 FR 12652), which required the submission of new drug applications as a condition for continued marketing of amphetamines, 106 new drug applications for amphetamines or amphetamine-containing drug products were received. The data submitted in those applications, and data obtained from other sources concerning anorectic drugs, generally supported the efficacy of anorectic drugs.

(b) On the basis of currently available evidence derived from short-term studies, the Commissioner concludes that single drug entity oral dosage forms of amphetamine or dextroamphetamine are effective in the management of exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction, based on caloric restrictions, for patients in whom obesity is refractory to other measures. For purposes of this regulation, a mixture of dextroamphetamine and amphetamine is ordinarily regarded as a single drug entity.

(c) The Food and Drug Administration is not aware of data providing substantial evidence of the effectiveness of levamfetamine and its salts and regards these preparations as new drugs requiring approved full new drug applications.

(d) In view of the well-documented history of abuse of parenteral amphetamines, the severe risk of drug dependence, and the availability of safer alternative parenteral drugs which are equally effective for recognized non-anorectic indications, the Food and Drug Administration regards parenteral amphetamines as lacking evidence of safety.

(e) Any combination drug containing amphetamine or dextroamphetamine is regarded as a new drug requiring an approved full new drug application as a condition for marketing. Data in new drug applications are required to fulfill the criteria set forth in § 300.50 of this

chapter governing fixed combination prescription drugs for humans.

(f) New drug applications have been received from persons marketing orally administered single entity amphetamine or dextroamphetamine dosage forms. Any other person who intends to market such drug is required to submit to the Food and Drug Administration an abbreviated application under § 314.55 of this chapter.

(g) The labeling conditions for single entity oral dosage forms of amphetamine and dextroamphetamine and their salts are as follows:

(1) The label shall bear the statement “Caution: Federal law prohibits dispensing without prescription”.

(2) The drug shall be labeled to comply with all requirements of the act and regulations. The labeling shall bear adequate information for safe and effective use of the drug. The indications for use are:

Narcolepsy.

Minimal brain dysfunction in children (hyperkinetic behavior disorders), as an aid to general management.

Management of exogenous obesity as short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, for patients in whom obesity is refractory to other measures.

(3) Complete labeling guidelines are available from the Food and Drug Administration.

(h) Regulatory proceedings will be initiated with regard to any such drug within the jurisdiction of the act which is not in accord with this regulation.

[39 FR 11680, Mar. 29, 1974, as amended at 41 FR 10885, Mar. 15, 1976; 55 FR 11578, Mar. 29, 1990]

§ 310.506 Use of vinyl chloride as an ingredient, including propellant, of aerosol drug products.

(a) Vinyl chloride has been used as a propellant in aerosol drug preparations. Evidence indicates that vinyl chloride inhalation can result in acute toxicity manifested by dizziness, headache, disorientation, and unconsciousness where inhaled at high concentrations. Cardiac effects, bone changes, and degenerative changes in the brain, liver, and kidneys have been reported in animals. Studies also demonstrate carcinogenic effects in animals as a re-

sult of inhalation exposure to vinyl chloride. Recently, vinyl chloride has been linked to liver disease, including liver cancer, in workers engaged in the polymerization of vinyl chloride.

(b) The Commissioner finds that there is a lack of general recognition by qualified experts of the safety or effectiveness of aerosol drug preparations containing vinyl chloride as an ingredient, including propellant. Therefore, any such product containing vinyl chloride is a new drug and a new drug application approved under section 505 of the Federal Food, Drug, and Cosmetic Act is required for marketing.

(c) Clinical investigations designed to obtain evidence that any aerosol drug preparation containing vinyl chloride as an ingredient, including propellant, is safe and effective for the purpose intended, must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Any such drug within the jurisdiction of the act which is not in accord with this regulation is subject to regulatory action.

[39 FR 30830, Aug. 26, 1974, as amended at 55 FR 11578, Mar. 29, 1990]

§ 310.507 Aerosol drug products for human use containing 1,1,1-trichloroethane.

(a) Trichloroethane has been used in aerosol drug products as a solvent for the active ingredients and to reduce the vapor pressure of the propellants. It is potentially toxic to the cardiovascular system, i.e., can sensitize the heart to epinephrine. At a sufficiently large concentration, it is a potent anesthetic agent. Deaths associated with aerosol decongestant products intended to be inhaled and containing trichloroethane have been reported. Most of the deaths resulted from abuse or gross misuse of the preparations.

(b) The Food and Drug Administration finds that there is a lack of general recognition by qualified experts of the safety or effectiveness of trichloroethane in aerosol drug products intended for inhalation either directly or indirectly. Any aerosol drug product containing trichloroethane and labeled, represented, or advertised for